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13. ABSTRACT (Maximum 200 Words)

Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Suspected causes for these health complaints continue to be investigated and include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. Many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. It is the goal of this study to further evaluate the role of pesticides in the development of symptoms reported by GW veterans. This will be accomplished by performing neuropsychological assessments with a group of military pesticide applicators. It is hypothesized that pesticide applicators with high exposures will perform significantly worse on cognitive and neurological measures than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides) will prove to be synergistic and/or additive in terms of decreased cognitive and neurological functioning and increased physical symptoms.

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INTRODUCTION

Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Research to date suggests that it is unlikely that there is one single cause for GW illness but rather suggests that multiple causes in different groups of veterans is the likely the cause of continued health symptoms. Suspected causes for GW veterans continued health complaints include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. Research evaluating the effects of pyridostigmine bromide (PB) exposure on neuropsychological functioning in GW veterans, found significantly lower performance on tasks assessing executive system functioning in the PB exposed GW veterans compared with controls (Sullivan et al., 2003). Pesticide exposure has been associated with mood decrements and residual effects many years after exposure in a large longitudinal cohort of GW veterans (White et al., 2001). In addition, low-level nerve agent exposure (from Khamisiyah weapons arsenal) has been associated with mood complaints and executive system decrements in GW veterans (White et al., 2001).

It has been documented that many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. For example, recent studies of agricultural workers and professional pesticide applicators have found lasting deficits in neurological and cognitive functioning resulting in decreased processing speed and mood complaints (Stephens et al., 1995; Steenland et al., 1994).

It is the goal of this study to further evaluate the role of pesticides in the development of CNS symptoms reported by GW veterans and to assess the additive and/or synergistic effects of combinations of chemical exposures and stress. This will be accomplished by assessing a group of military pesticide applicators with known chemical exposures. It is hypothesized that applicators with high exposures will perform significantly worse on specific cognitive and

neurological measures and report more health symptom complaints than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides, low-level nerve agents) will be synergistic and/or additive in terms of decreased cognitive and neurological functioning.

The specific aims of this study are: (1) To determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans (2) To determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans (3) To assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

Body

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide.

Task 1. Develop Plan for Subject Recruitment Months 1-6:

a. Locate and obtain previous exposure interviews from a group of Gulf War veteran pest-control interviewees (PCI) previously contacted by Office of the Special Assistant to the Under Secretary of Defense for GW illnesses (OSA) in 1997-1998 (months 1-3).
b. SRBI, an independent contracting company (with an 80% success rate) will contact all PCIs and obtain current address and administer a brief follow-up questionnaire (months 3-4).
c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure (months 3-5).
d. Identify pool of potential subjects for each of four exposure categories to recruit (months 4-5).
e. Screen potential subjects for exclusion criteria (months 5-6).

Task 2. Perform Subject Recruitment and Data Collection Months 6-42:

a. Study coordinator will contact potential subjects for recruitment and arrange for travel to multiple study sites (months 6-42).
b. Perform cognitive evaluations and psychodiagnostic interviews from 160 study participants (months 6-42).
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for all study subjects (months 6-42).

Task 3. Data Collection and Interim Analyses, Months 18-42:

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing (months 18-42).
b. Interim Statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically (months 18-42).
c. Exposure assessment analyses for pesticides and PB will be ongoing (months 18-42).
d. Annual reports of progress will be written (12-36).

Task 4. Final Analysis and Report Writing, Months 42-48:

a. Analyze subject characteristics of individuals who were lost to follow-up (months 42-44).
b. Write final study report and prepare manuscripts for submission (months 44-48).

The statement of work for year 1 is below and primarily describes the completion of the start-up phase of the study including obtaining the study sample from a group of pest control interviewees (PCIs) previously interviewed by the Deployment Health Support Directorate (DHSD), to obtain current contact information for the PCIs and administer a brief follow-up questionnaire with these individuals. In addition, in year 1, the plan was to recruit 20 study participants for the study protocol including cognitive evaluations, psychological interviews and exposure questionnaires.

Statement of work for Year 1:

Task 1. Develop a Plan for Subject Recruitment (as stated above):

a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly the OSA) conducted in 1997-1998.
b. Contract with an outside survey company, SRBI, to contact PCIs and obtain current address and administer a brief follow-up questionnaire.
c. Categorize PCIs into high and low exposure groups based on the telephone surveys.
d. Identify pool of potential subjects for each of four exposure categories to recruit.
e. Screen potential subjects for exclusion criteria.

Task 2. Perform Subject Recruitment and Data Collection (specific to year 1):

a. Recruitment of 20 study subjects and arrange for travel to multiple study sites
b. Perform cognitive evaluations and psychodiagnostic interviews with 20 study participants
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 20 study subjects by study questionnaires.

Task 1a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly OSAGWI) conducted in 1997-1998.

The Pesticides Environmental Exposure Report (www.gulflink.osd.mil) commissioned by the Deployment Health Support Directorate provided estimates of exposure for general deployed military and separately for pesticide applicators from the Gulf War based on interviews with the current study sample of pesticide applicators and preventive medicine specialists and a review of DOD pesticide records.

The term "pest control interviewee" (PCI) refers to any of the 298 personnel interviewed by the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) in the course of the "preventive medicine" (PM), "delousing," and other interviews described in OSAGWI's Pesticides Environmental Exposure Report. OSAGWI chose to interview these individuals because it was believed that they would be the most likely to have knowledge of pesticide products used in the Army, Navy, Air Force, and Marines. They were identified based on military occupational specialty (MOS) codes. PCIs include physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police, and other pest controllers. OSAGWI has since been renamed the Deployment Health Support Directorate (DHSD).

The current study is an examination of the CNS effects of neurotoxicant exposure in pest control interviewees (PCI) with known neurotoxicant exposures as a result of their tour of duty at the time of the Gulf War. PCI's comprise specific groups of GW veterans likely to fall into high and low categories of pesticide exposure based on their military occupational specialty (MOS). Each potential participant previously completed a pesticide interview that included self-report measures of exposures to neurotoxicants while in the Gulf region. PCI contact information and interview data (conducted in 1997-1998) were provided to the Principal Investigator by Dr. Michael Kilpatrick, M.D., Deputy Director of the Deployment Health Support Directorate

(previously known as OSAGWI) through their System of Records Notice which permits release of records to the Veterans Administration. The DHSD released the records to the VA Boston Healthcare System through a Memorandum of Understanding (MOU). The MOU provided assurances from the VA Boston Healthcare System and the Boston Environmental Hazards Center (a joint program of the VA Boston Healthcare System and Boston University).

The MOU states:

1) The released PCI records will only be used for the purposes of the current study

2) Only study personnel will have access to the released records

3) The released information will be safeguard to preserve the confidentiality of the data

4) Any personal identifiers will be removed from any interim and final reports that are prepared as a consequence of this study.

The PCI interview records were used in conjunction with current interview data to categorize individuals into high and low pesticide and PB (pyridostigmine bromide) exposure categories. In addition, these interviews will also be used in conjunction with the current exposure questionnaires to perform dose-estimates for pesticides and PB. Mr. William Bradford, lead author of the Pesticides Environmental Exposure Report, will be available to assist with these dose-estimates in years 2-4.

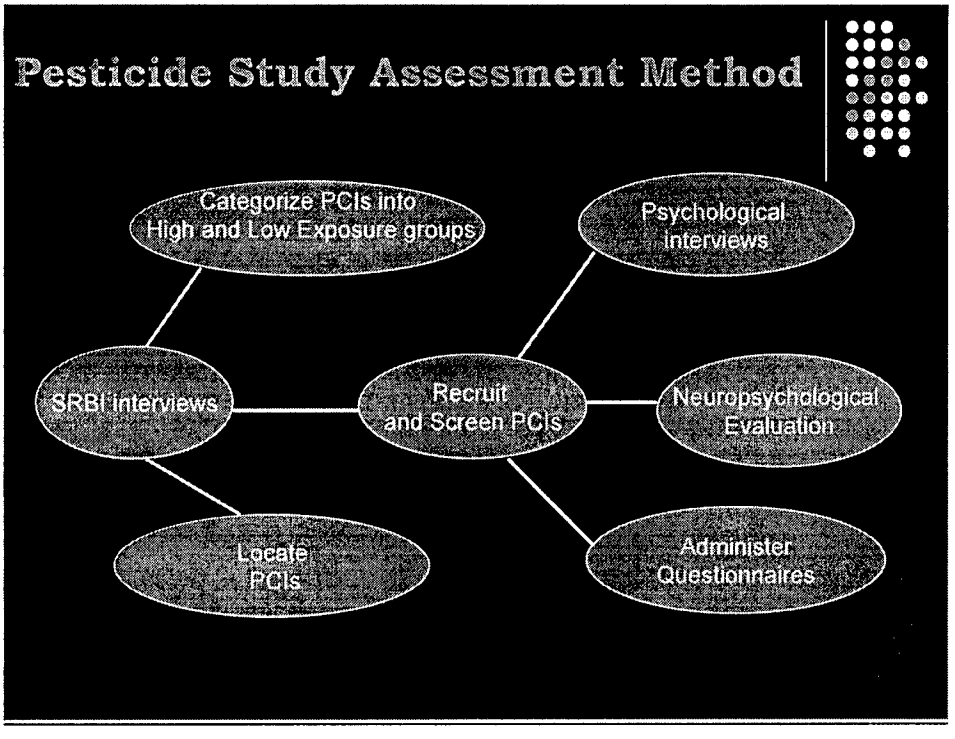
Task 1 b. SRBI, an independent contracting company will contact PCIs and obtain current address and administer a brief follow-up questionnaire.

An outside research firm (Schulman, Ronca, & Bucuvalas, Inc., SRBI) with extensive experience collecting data from veterans of the U.S. Armed Forces was subcontracted to obtain current telephone numbers and addresses for the PCIs and to administer a brief follow-up questionnaire by telephone. The recruitment process was as follows: PCIs were sent a letter from the PI explaining that SRBI would be contacting them to conduct a brief telephone interview and

obtain their current contact information for the study. A postage paid opt-out postcard was included with this introduction letter. If the PCI elected to return this postcard, there was no further contact with this individual for the study. If a postcard was not returned to the study staff, SRBI attempted to contact the PCI and determine if they wished to participate in the brief interview regarding their pesticide and PB exposures during the Gulf War. Ten individuals returned the opt-out postcards and were not contacted further for this study. From the remaining list, SRBI was successful in completing 160 telephone interviews with PCIs regarding neurotoxicant exposures resulting in a live refusal rate of just seven percent. SRBI was also able to find current contact information for all 293 PCIs and identify that one PCI was deceased.

The study design is presented in the figure below followed by tables of demographic information computed from the SRBI telephone interview data.

Figure 1. Pesticide Study Assessment Design



From the SRBI telephone interviews, demographic and exposure data was collected from each responding PCI. The demographic information is reported in table 1. From this group of 160 study respondents, 140 were male and 20 were female. The average age for the group of Gulf War veterans was 48 years old and the group was largely Caucasian (85%). The most commonly reported current health problems reported by these study participants were hypertension, cardiovascular disease, arthritis, asthma, back and joint pain, skin rash and memory problems. When broken down into groups based on high and low groups for pesticides and PB, the only notable differences were found in increased reporting of hypertension (12 vs. 6 PCIs), cardiovascular disease (6 vs. 2 PCIs) and arthritis (6 vs. 1 PCI) in the high pesticide group compared with the low pesticide group. While the high and low PB groups did not appear to differ very much with respect to health symptom reporting from this brief health query included in the telephone interviews. The larger study questionnaire with more in-depth questions regarding medical diagnoses will help to better characterize these groups in terms of health outcomes and show their significance. The demographic breakdown of the SRBI surveys is reported in table 1.

Table 1. Demographic Breakdown for SRBI Survey Respondents

Gender	Frequency	Percent
Male	140	87.5
Female	20	12.5
Total	160	100

Current Age for SRBI Survey Respondents

Minimum	Maximum	Mean
33	74	47.7

Ethnicity for SRBI Survey Respondents

Ethnicity	Frequency	Percent
African American	12	7.5
Asian American	3	1.9
Caucasian	136	85.0
Hispanic American	6	3.8
Other	3	1.9

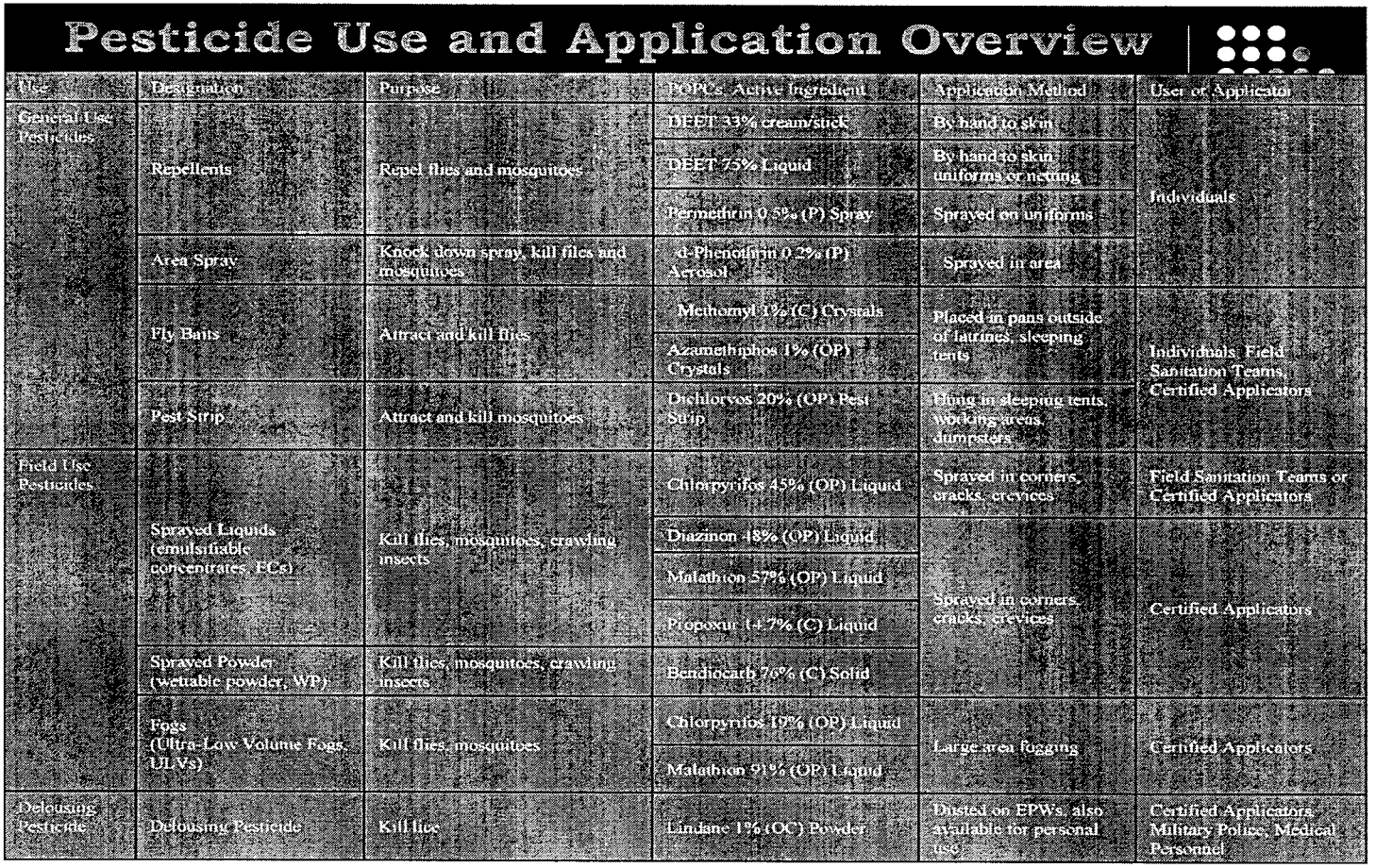
Health Symptom Self-report for SRBI Respondents

Symptom	Frequency	Percent
Hypertension	23	14
Cardiovascular Disease	11	7
Arthritis	12	8
Asthma	10	6
Back Pain	11	7
Joint Pain	13	8
Skin Rash	14	9
Memory Problems	14	9

Task 1 c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure.

Pesticides were used widely in the Gulf War to protect troops from such pests as sand flies, mosquitoes and fleas that can carry the infectious diseases leishmaniasis, sand fly fever and malaria. Indeed, of the nearly 700,000 US troops deployed to the Gulf region, only 40 cases of infectious diseases were documented (Winkenwerder Jr, W., 2003). US forces used pesticides in areas where they worked, slept, and ate throughout the GW. In fact, on any given day during their deployment, GW veterans could have been exposed to 15 pesticide products with 12 different active ingredients and pesticide applicators were likely exposed to more pesticide products and at higher doses. Troops used pesticides for a number of reasons, including personal use on the skin and uniforms as an insect repellent, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, and as delousing agents applied to enemy prisoners of war. These widespread, commonly reported uses supported the decision by the OSAGWI to investigate pesticide exposures as a potential contributor to unexplained illnesses in GW veterans. According to the OSAGWI report, the pesticides of potential concern (POPCs) used by US military personnel during the GW can be divided into five major classes or categories:
1) organophosphorus pesticides, such as malathion and chlorpyrifos; 2) carbamate pesticides, such as bendiocarb; 3) the organochlorine, lindane; 4) pyrethroid pesticides, such as permethrin; and 5) the insect repellent DEET (see figures 2 through 4).

Figure 2. Pesticide use and Application Overview.



Pesticide Use and Application Overview

Use	Designation	Purpose	POPCs Active Ingredient	Application Method	User or Applicator
General Use Pesticides	Repellents	Repel flies and mosquitoes	DEET 33% cream/stick	By hand to skin	Individuals
			DEET 75% Liquid	By hand to skin, uniforms or netting	
			Permethrin 0.5% (P) Spray	Sprayed on uniforms	
	Area Spray	Knock down spray, kill flies and mosquitoes	d-Phenothrin 0.2% (P) Aerosol	Sprayed in area	
	Fly Baits	Attract and kill flies	Methomyl 1% (C) Crystals	Placed in pans outside of latrines, sleeping tents	Individuals, Field Sanitation Teams, Certified Applicators
			Azamethiphos 1% (OP) Crystals		
	Pest Strip	Attract and kill mosquitoes	Dichlorvos 20% (OP) Pest Strip	Hung in sleeping tents, working areas, dumpsters	
Field Use Pesticides	Sprayed Liquids (emulsifiable concentrates, ECs)	Kill flies, mosquitoes, crawling insects	Chlorpyrifos 45% (OP) Liquid	Sprayed in corners, cracks, crevices	Field Sanitation Teams or Certified Applicators
			Diazinon 48% (OP) Liquid	Sprayed in corners, cracks, crevices	Certified Applicators
			Malathion 57% (OP) Liquid		
			Propoxur (4.7% (C) Liquid		
	Sprayed Powder (wettable powder, WP)	Kill flies, mosquitoes, crawling insects	Bendiocarb 76% (C) Solid		
	Fogs (Ultra-Low Volume Fogs, ULVs)	Kill flies, mosquitoes	Chlorpyrifos 19% (OP) Liquid	Large area fogging	Certified Applicators
			Malathion 91% (OP) Liquid		
Delousing Pesticide	Delousing Pesticide	Kill lice	Lindane 1% (OC) Powder	Dusted on EPWs, also available for personal use	Certified Applicators, Military Police, Medical Personnel

Figure 3. Active ingredients in pesticides of potential concern.

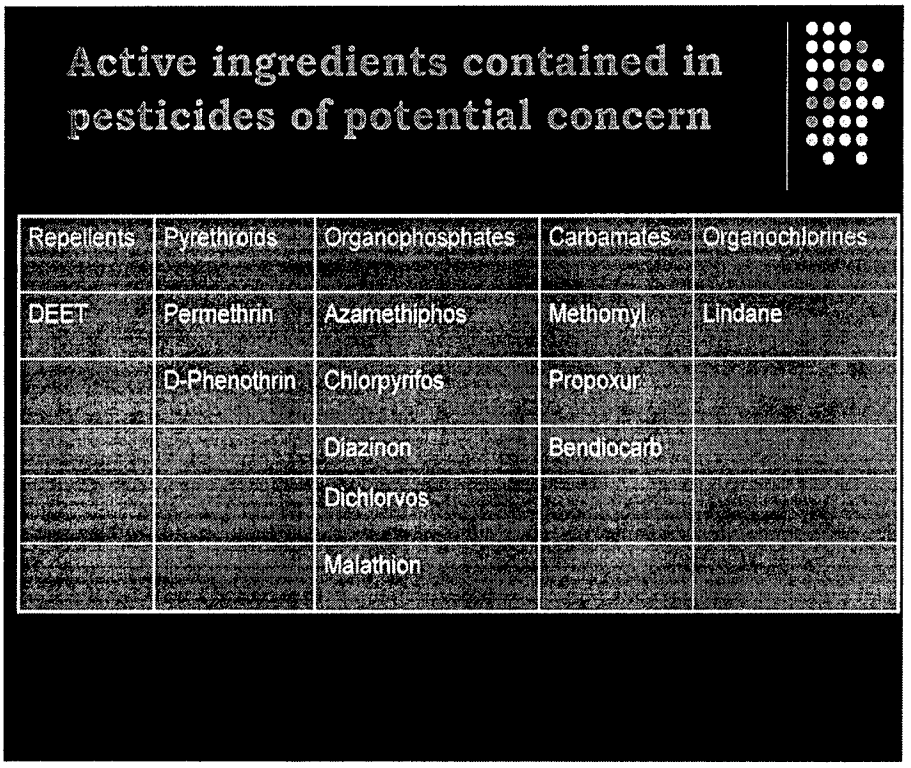
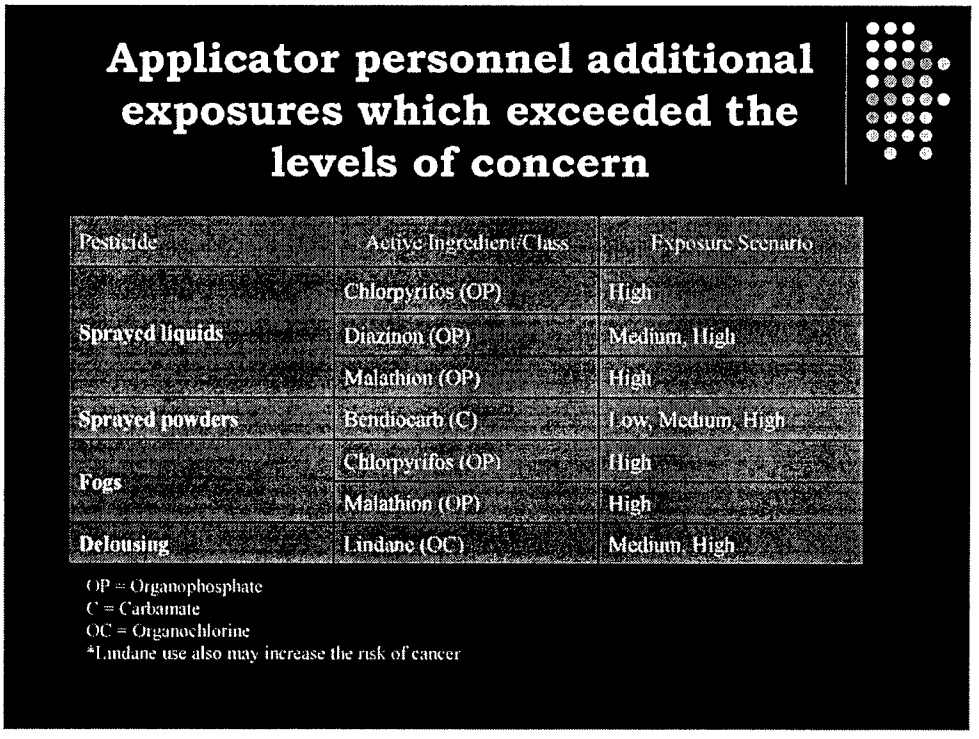


Figure 4. Applicator exposure levels reaching levels of concern



Guidelines for pesticide and PB exposure are presented in the tables 2 and 3 and were used to classify participants into high and low exposure categories based on prior OSAGWI interviews and current interviews conducted by SRBI.

Table 2. Guidelines for Pesticides

Low exposure

An individual is assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below. For example, an individual exposed to pyrethroids other than via fogs, but no other pesticides, would be assigned to a low pesticide exposure group.

High exposure

An individual is assigned to the high-exposure category for pesticides if any of the following apply:

1) PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, other than minor skin irritation, at least once. A general statement, such as "became ill" will qualify.

2) PCI probably applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits (≥2 pounds handled), and/or fogs. PCI may or may not have worn adequate personal protective equipment (PPE).

3) PCI was probably present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.

4) PCI probably spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.

5) PCI probably applied DEET to self at least 30 times. PCI must provide enough information to conclude that usage was equivalent to or above this level. DEET application 30 times per month is the 25th percentile value determined by the RAND (2000) survey for ground forces who used DEET (50% reported no use).

Table 3. Guidelines for PB

Low exposure

An individual is assigned to the low-exposure category for PB if no acute signs and/or symptoms of exposure were reported *and* any of the following apply:

1) The individual reported not using PB.

2) The total dose reported was less than or equal to 180 mg PB active ingredient.

3) The individual reported using PB, but could not recall sufficient details to conclude that the dose was probably greater than 180 mg PB active ingredient.

High exposure

Individuals are assigned to the high-exposure category for PB if either of the following apply:

1) The total dose was probably greater than 180 mg PB active ingredient.

2) The individual reported taking any PB and also reported experiencing acute signs and/or symptoms of exposure.

PB and pesticide exposure were categorized as high and low based on the previous OSAGWI interviews and the current SRBI interviews. From these interviews, 97 PCIs were categorized in the high pesticide exposure group and 63 PCIs were categorized in the low pesticide exposure group and 81 PCIs were categorized in the high PB group and 79 PCIs were categorized in the low PB group. Additional categorization for pesticide and PB exposure and Khamisiyah notification (identifying those potentially exposed to chemical weapons) are listed in table 4.

Table 4. PB and Pesticide Exposure Categories

Self-reported PB Exposure during the Gulf War		
	Frequency	Percent
Yes	118	74
No	33	20
Don't Know	9	6
Total	160	100
Self-reported Pesticide Exposure during the Gulf War		
	Frequency	Percent
Yes	122	76
No	30	19
Don't Know	8	5
Total	160	100
Exposure Categories for PB and Pesticides		
	PB	Pesticides
Low	79	63
High	81	97
Total	160	160
Khamisiyah Weapons Depot Notification		
	Frequency	Percent
Yes	59	37
No	101	63
Total	160	100

Task 1 d. Identify pool of potential subjects for each of four exposure categories to recruit.

Combining the previously described high and low exposure groups for the pesticide and PB groups allowed for four category groupings (table 5). The categories include high pesticide and high PB exposure, high pesticide and low PB, low pesticide and high PB, and low pesticide and low PB. The goal of the study was to recruit 40 study participants from each of the four exposure categories with the study participants sequentially assigned to one of the four study groups based on exposure combination. However, the high pesticide/low PB (n =37) and the low pesticide/high PB (n = 20) groups appear to be smaller than expectation and may not allow for such large groupings (table 5). However, analyses controlling for different exposure groups will be employed to control for different group sizes if necessary.

Table 5. Four Exposure Categories for PB and Pesticides

	Pesticide categories		
PB categories	**Low**	**High**	**Total**
Low	**42**	**37**	**79**
High	**20**	**61**	**81**
Total	**62**	**98**	**160**

Task 1 e. Screen potential subjects for exclusion criteria.

The exclusion criteria for this study include current substance abuse, substantial traumatic brain injury or other documented neurological illness precluding the use of a computer. Prior substance abuse and current medications are recorded but do not constitute exclusion criteria. These exclusion criteria were chosen so that study participants who may perform poorly on cognitive testing for known reasons other than environmental exposures could be screened out to prevent potential study confounders.

From the SRBI telephone interviews, a review of reported health symptoms was performed and no participant from these interviews reported significant head injury or other significant neurological illness that might interfere with performing the cognitive and computer testing parts of the study protocol. There was one case reported of a brain tumor recently removed and a case of multiple sclerosis (MS). However, the study participant with MS was one of the first recruited study participants for the cognitive evaluations and was able to complete the entire study protocol. In the first recruitment trip, none of the study participants were screened out.

Subject recruitment is ongoing and PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain a serious brain injury. Screening for exclusion criteria occurs during the telephone recruitment phase of the study and will be ongoing during the study recruitment efforts.

Task 2a. Recruitment of 20 study subjects and arrange for travel to multiple study sites.

Twelve study participants were recruited and have completed the study protocol (cognitive evaluation, psychological interviews and exposure questionnaires). This group included 11 men and 1 woman. The exposure classifications for this group included 5 high pesticide, 7 low pesticide, and 4 high PB, 8 low PB categories. Although 20 study subjects were originally projected to be recruited for Year 1, a slow start-up phase resulting predominantly from delays in obtaining all the appropriate human subjects approvals resulted in time for one large recruitment trip during Year 1. This trip was quite successful and resulted in only two refusals from reachable potential participants from that geographic area (St. Louis, MO).

The current address for each PCI was obtained by SRBI during their telephone interviews and the breakdown by state is listed in Table 6. This information will enable better planning for recruitment trips to these locations. The recruitment strategy will be to target the more populated areas first. The next planned recruitment trips will be in Florida followed by Virginia and Maryland. It is anticipated that the recruitment of 58 additional study participants (50 projected for Year 2 plus 8 from Year 1 projections) will be obtainable by the end of Year 2 for a total of 70 recruited study participants. Given the favorable response from the first recruitment efforts, major difficulties with subject recruitment are not anticipated at this time.

Table 6. PCI Current Residence by State

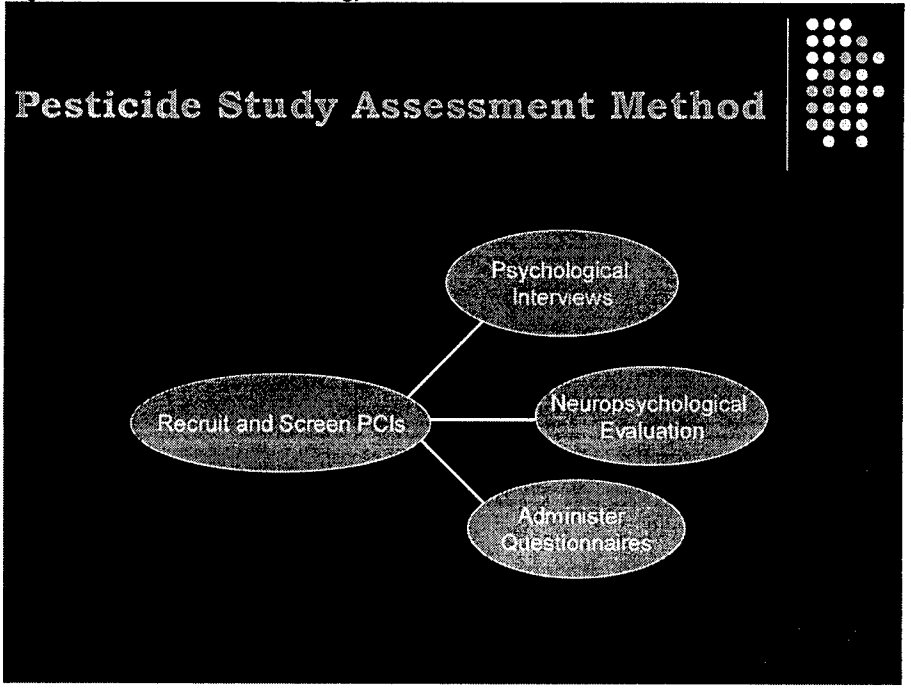
AK	1	MN	1
AL	5	MO	23
AR	6	MS	3
AZ	4	MT	2
CA	9	NC	14
CO	9	NE	5
CT	1	NJ	2
DC	1	NM	3
DE	1	NY	8
FL	24	OH	4
GA	12	OK	3
GU	1	OR	1
HI	4	PA	8
IA	2	RI	2
IL	3	SC	6
IN	1	TN	15
KS	6	TX	20
KY	2	UT	2
LA	2	VA	17
MA	3	WA	13
MD	10	WI	9
ME	1	WV	1
MI	9	Active duty	14

Recruitment Methodology

When recruiting study participants, the PI or study staff contact PCIs participating in the SRBI interviews to describe the study and establish whether the PCI will participate in the cognitive evaluation. The initial contact with the study staff consists of a description of the study, describing the types of assessment, time required, and reimbursement for their time and effort. Subjects have an opportunity to ask questions about the procedure. They are informed that whether or not they participate will have no bearing on their medical care and that, if they choose to participate, they may withdraw at any time without prejudice. They are asked to indicate whether they wish to participate, wish not to participate, or wish to defer this decision. In the latter case they are asked whether we may contact them again to

determine their decision. Gulf War veterans who are currently on active duty are contacted at home in the evening hours and will not be contacted during duty hours. Active duty PCIs are not be compensated for their participation as there are restrictions on compensation to active duty personnel. PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for alcohol or other substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain serious brain injury). Prior substance abuse and current medications are recorded but do not constitute exclusion criteria. An appointment during one of the field trips is scheduled for subjects agreeing to participate. PCI veterans retained in the study sample are presented the study consent form for signature. The study methodology is presented in figure 5.

Figure 5. Recruitment Methodology.



Task 2b. Perform cognitive evaluations and psychodiagnostic interviews with 20 participants

The goal for year 1 was to recruit and perform cognitive and psychodiagnostic interviews with 20 study participants. As described above, a total of 12 study participants were recruited in year 1 due to a slow start-up phase for the study. However, all twelve of the study participants completed the entire study protocol and did not express any difficulties with the length of the examination. The cognitive evaluations were completed in 1.5 hours for most of the study participants and the psychodiagnostic interviews required an additional twenty minutes in most cases to complete. Study participants are able to take breaks during the study protocol session if they feel they need them and can fill out their questionnaires and mail them back if necessary. With this strategy, it is not anticipated that there will be much missing data from the study protocols. However when missing data is encountered during data analysis, interpretative statistics will be employed whenever possible.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in the tables 7 and 8 followed by a description of the study instruments and procedures.

Table 7. Definitions of Neuropsychological Domains

I. General Intelligence: IQ scores in all domains or in a specific domain (verbal or visual-motor); academic skills; performance on tests of reading, spelling, arithmetic, vocabulary, academic knowledge.
II. Attention, Executive System: Capacity to focus on incoming stimuli; includes vigilance, tracking and capacity to divide attention between competing stimuli.
III. Motor: Speed and dexterity in completing tasks.
IV. Visuospatial function: Processing of nonverbal information such as visual designs, visual constructions, and geographic information; includes sequencing, organization (mental) and constructional ability.
V. Memory: Anterograde memory function involves encoding, storing, retrieving and retaining new information. Retrograde memory function refers to ability to recall information learned in the past.
VI. Mood/Personality: Includes temporary and characterologic mood states and characterologic personality traits or tendencies.
VII. Motivation and Malingering: An evaluation of effort.

Table 8. Full Neuropsychological Test Battery.		
TEST NAME	**DESCRIPTION**	**OUTCOME MEASURE**
I. Tests of Premorbid Functioning		
Wechsler Adult Intelligence Scale-Revised (WAIS-III; Wechsler, 1997) Information subtest	Information usually learned in school; to assess native intellectual abilities	Raw Score
Boston Naming Test (BNT; Kaplan et al., 1983)	Confrontation naming of line drawings; to assess verbal abilities	Raw Score
II. Tests of Attention, Vigilance and tracking		
Trail-making Test (Reitan &Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)	Completion
Computerized Continuous Performance Test (CPT; Letz & Baker,1988)	Target letter embedded in series of distractors; to assess sustained attention and reaction time	Reaction Time Total Errors
Wisconsin Card Sorting Test (WCST; Heaton et al, 1993)	Requires use of feedback to infer decision making rules; assesses problem solving ability and flexibility	Total # Sorts
III. Tests of Motor Function		
Finger Tapping Test (Reitan & Davidson, 1974)	Speed of tapping with index finger of each hand; assesses simple motor speed	Mean Taps
Grooved Pegboard Test (Klove, 1963)	Speed of inserting pegs into slots using each hand separately; assesses motor coordination and speed	Raw Score
IV. Tests of Visuospatial Function		
Hooper Visual Organization Test (HVOT; Hooper, 1958)	Identifying objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli	Raw Score
Rey-Osterreith Complex Figure (ROCFT; Corwin &Blysma, 1993)	Copying a complex geometric design; assess ability to organize and construct	Raw Score

TEST NAME	DESCRIPTION	OUTCOME MEASURE
V. Tests of Memory		
California Verbal Learning Test (CVLT; Delis et al., 1987)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies	Total Trials 1-5 Long Delay
ROCFT-Immediate and 20 minute recall	Immediate and Delayed recall of a Complex figure	Raw Score
Stanford-Binet Copying Test (Terman & Merrill, 1973)	Immediate and 10 minute delay of 16 designs	Raw Score
VI. Tests of Personality and Mood		
Profile of Mood States (POMS; McNair et al., 1971)	65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales	T-Scores
VII. Tests of Motivation		
Test of Motivation and Malingering (TOMM; Tombaugh, 1996)	Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering	Raw Score

Assessment Instruments and Procedures

1. Cognitive Assessment.

A tester who is blind to the exposure status of the subject administers the neuropsychological test battery. The neuropsychological test battery assesses the functional domains of general intelligence, attention, executive abilities, motor function, visuospatial skills, memory, and mood (table 7). The battery is described in detail in Table 8. It includes 1) tests designed to tap relatively stable native intellectual abilities including the Information subtest from the WAIS-III, and the Boston Naming Test. On these tests, it is expected that the scores will be consistent with estimated native IQ based on age, education, and occupational history and 2) tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions that have in past studies demonstrated utility in the assessment of toxicant-induced brain damage, and psychiatric disorders. The domains included in this category are attention and executive function, motor skills, mood and memory.

Sustained attention is measured by number of errors on a test of continuous performance (CPT), a computer-assisted test from the Neurobehavioral Evaluation System (NES), an instrument widely used in the field of occupational health, that represent adaptations of traditional neuropsychological instruments for computerized stimulus presentation and recording of responses. The NES instruments have reliable psychometric properties and have demonstrated validity in epidemiological and laboratory studies of exposure to a wide variety of neurotoxicants. Also used as measures of executive functioning, are measures of cognitive flexibility (Wisconsin Card Sort test) and alternation of set (Trail making test, part B).

Motor functioning is measured by the mean of five trials on each hand on the finger tap test, the time to completion on the grooved pegboard test and reaction time on the CPT test.

Previous studies of occupational pesticide exposure have documented changes in reaction time and motor speed (NCTB). Therefore, we predict decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures.

The test battery also includes the Profile of Mood states as a self-report assessment of current mood. The indicators of importance are current fatigue, confusion, tension and depression. Mood has been shown to be associated with changes in subcortical-limbic system and neurotransmitters as a result of toxicant exposures and as such, mood will be treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we will administer the Rey-Osterrieth Complex Figure Test and document total scores for the copying subtest (rey-osterrieth scoring out of 36). We expect that individuals with increased exposures will have difficulty maintaining the overall configuration, tremulous writing and segmentation as a result of basal ganglia dysfunction commonly seen in these people. In addition, the Stanford Binet copying task will be used in this test battery to document further impairment in visuoconstruction as has been found in our prior research. The total score for copying (out of 16 possible) is expected to be diminished in those who have significant neurotoxicant exposures.

Individuals who have documented exposures to neurotoxicants have had difficulty in the areas of acquisition and retrieval. Therefore, we will be examining verbal and nonverbal memory with the use of the Rey-Osterrieth Complex Figure Immediate and Delayed recall and the CVLT-II measures of total recall trials 1 to 5 (raw score) and Long-delay free recall (raw Score).

Lastly, a measure to response consistency will be used to document the possibility of diminishment in motivation. Raw scores (out of a possible score of 50) will be computed and we expect that only a few individuals will fall below a score of 45 (indicating decreased motivation). In the event of decreased motivation scores on this test, analyses will be performed with and without these individual's test scores to assess for potential differences. If there are

significant differences between the groups, then the group with low motivational scores will be removed from the dataset.

Because this study compares neuropsychological functioning in pesticide exposed individuals many years after their GW exposures, the question arises how does one decide if decreased performance in cognitive functioning is actually associated with pesticide exposure or if those individuals with cognitive deficits simply report more pesticide exposure. One way to examine this problem with self-reported exposures and correlating them with current brain functioning is by comparing patterns of cognitive performance in relation to the reported exposure. The field of behavioral neurotoxicology is an established field that studies the effect of brain/behavior (test performance) relationships and specific types of neurotoxicant exposures.

Epidemiological studies during the past 30 years have examined the impact of exposure to metals (e.g., lead, mercury, arsenic), organic solvents (e.g., trichloroethylene, n-hexane, petroleum distillates), and pesticides (e.g., organophosphates, carbamates) on brain functioning and found different cognitive patterns with these exposures. For example, studies of solvent exposure have reliably shown disturbances in executive function, attention, visuospatial skills, short-term memory, and mood (Anger, 1990, White et al., 1992 and Echeverria& White, 1992) Studies of lead-exposed workers have yielded similar findings along with decrements in verbal reasoning and motor functions (Baker et al., 1984, Hanninen et al., 1978 and Yokoyama et al., 1988). While studies of pesticide-exposed agricultural workers have shown disturbances in processing speed and mood and sequelae from overt poisoning from organophosphate pesticides can result in lasting deficits in the domains of visuomotor, attention/executive functioning, motor functioning and mood. Therefore, we would be comparing not only specific test performance to self-report of pesticide exposure but also the pattern of cognitive performance in the domains of attention/executive functioning, memory, visuospatial skills, motor skills and mood.

In addition to exposure class, other factors (e.g., age, education, intelligence, prior exposures, medical and health concerns, alcohol abuse, life stress, and workplace stress) are likely to influence performance on cognitive tests (Grasso et al., 1984, Hanninen, 1988, Proctor et al, 1996 and Letz, 1993.) and must be taken into account in evaluating the effects of exposure to known or suspected toxicants. Therefore, the study was designed to be able to compare cognitive patterns on five different domains in individuals reporting higher and lower pesticide exposures (table 7).

We have made specific hypotheses of how the higher pesticide exposed individuals will perform based on prior epidemiological studies showing the cognitive pattern of motor (performance speed) and mood decrements in pesticide exposed individuals. We have also included a series of questionnaires to the study protocol that will obtain demographic (age, education, gender, premorbid intelligence) and diagnostic variables (Post-Traumatic Stress Disorder, Major Depression etc.) that could affect cognitive performance and should be controlled for in any analyses comparing self-reported exposures to neurotoxicants. In addition, an exposure questionnaire is also included in the study protocol (SNAC) that queries for other types of neurotoxicant exposures that could affect cognitive performance (exposures from hobbies and post-military employment) that will also be used as control variables.

2. Psychological Assessment.

1) Subjects are administered the Structured Clinical Interview for DSM-IV (SCID) and a current Global Assessment of Functioning score is assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I disorders. Dr. Krengel who will also be blind to the exposure data administers the Clinician Administered PTSD Scale (CAPS), a state-of-the-art instrument for confirming the diagnosis of

current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties. Subjects fill out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PTSD checklist), and to identify traumatic events, military or civilian (Modified Life Events Checklist, Traumatic Events) (table 9).

2) Dr. Krengel also conducts a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Subjects are asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors.

Treatment of Data

The aims of this study are to determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans, to determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans, and to assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

We will examine the relationship between neurotoxicant exposure and neuropsychological performance through multivariate multiple regression. This will include indicator variables to account for group status (1 = High PB, High Pesticide, 2 = High PB, low Pesticide, 3 = Low Pesticide, High PB, 4 = low Pesticide, Low PB) as well as individual risk factors and intervening risk factors that might be related to outcomes. Additional analyses exploring the interactions between the exposures and neuropsychological outcome will be pursued. We will look at the relationship of stress and health symptoms through the multiple regression analyses as described above. Steps have been employed to minimize missing data including offering breaks during cognitive testing, allowing participants to complete questionnaires at home and mailing them back

and completing psychological interviews by telephone (when necessary due to time constraints or fatigue of study participants). However when data is not obtainable, the missing data will be interpolated statistically whenever possible by comparing means of similarly answered questions.

Task 2c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 20 study subjects by study questionnaires.

All twelve study participants recruited in year 1 completed the study questionnaire. The study questionnaire is comprised of several health and mental health scales. These include: the health symptom checklist, Brief Symptom Inventory (BSI), PTSD checklist (PCL), Modified Life Events Checklist (Traumatic events), Veterans Version of the SF12 (SF12V), and the pesticide exposure questionnaire (SRBI questionnaire). See Table 9 for questionnaire descriptions. During Human Subject's Research Review Board review (HSRRB) of our study protocol, it was suggested that the questionnaires were lengthy and in some places redundant. Therefore, parts of the study questionnaire were shortened to reduce the demand on the study participant (see appendix for updated SNAC questionnaire). Specifically, several pages from the SNAC questionnaire were removed because similar questions were asked in other parts of the questionnaire.

Table 9. Study Questionnaire Descriptions

Name	Description
Demographics	Subjects report information on age, education, gender, ethnicity, marital status, GW duty service (active vs. reserve/National Guard), military rank and current military status.
SF12V	Veterans version of the SF12 which compares functional health-related quality of life. It includes a physical component score and a mental component score.
Health Symptom Checklist (HSC)	A comprehensive list of 34 frequently reported health and mental health symptoms. The HSC determines how often in the past 30 days the health symptoms were experienced. Symptoms from nine body systems are assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological).
Medical Conditions	Included in this checklist is a list of 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it was diagnosed.
Brief Symptom Inventory (BSI)	The Global Severity index of the BSI is a summary index that represents the most sensitive single inventory indicator of a subjects' psychological distress level by combining information on a number of psychological symptoms and their intensity.
PTSD checklist (PCL)	A 17-item checklist following DSMIII-R or DSM-IV guidelines and is a structured interview for clinical diagnosis of PTSD.
Modified Life events checklist (Traumatic Events)	Modified version of the life events checklist to check for traumatic life events.
Structural Neurotoxicant Assessment Checklist (SNAC)	The SNAC assesses the degree of past exposure to neurotoxicants during civilian and military occupations includes questions pertaining to recent occupational and environmental exposures. Questions include length stay, geographical location, and environmental exposure during deployment (type, intensity, frequency, duration, locale).
Pesticide Exposure Questionnaire (SRBI brief questionnaire)	This telephone interview will be conducted by SRBI to obtain pesticide and PB exposure estimates. Questions include what pesticides were used during the Gulf War and what health problems that the respondent currently reports.
Telephone Recruitment form	This telephone recruitment form will be used by study staff to recruit and track responses for potential study participants. Questions include current medical diagnoses, medication use, and participation in other Gulf War related studies.

KEY RESEARCH ACCOMPLISHMENTS

- A pool of potential study participants was identified from a group of previously interviewed pest control personnel deployed to the Gulf War.
- Previous interviews by the Deployment Health Support Directorate (DHSD) regarding pesticide and pyridostigmine bromide (PB) exposure were obtained and used to classify these individuals into high and low exposure groups.
- Telephone interviews were performed and resulted in only a seven percent refusal rate of live calls and completion of the targeted 160 total completed exposure surveys of PCIs.
- Potential study participants were categorized based on current residence.
- Current health symptoms were identified and categorized into symptom clusters.
- PCIs responding to the SRBI interviews were categorized into high and low exposure groups for pesticides and PB and a pool of potential subjects have been targeted for recruitment based on residence location and exposure category.
- Twelve study participants were recruited and completed the entire study protocol including cognitive evaluations, psychological interviews and exposure questionnaires.
- The first study recruitment efforts were greeted with interest and willingness to participate by the contacted PCIs. This is encouraging for further recruitment efforts. It appears that GW veterans continue to be interested in responding to surveys regarding health symptoms and are cooperative when asked to complete neuropsychological evaluations.
- It was determined that the study design allows for collection of all relevant data and can be accomplished in several recruitment trips throughout the country.

REPORTABLE OUTCOMES:

Manuscripts in preparation: (from previous DOD funding sources)

1. Sullivan et al., Longitudinal Cognitive Functioning in Treatment-seeking Gulf War-era Veterans.
2. Krengel et al., Longitudinal Health Symptom Report in Treatment-seeking Gulf War-era Veterans.
3. Proctor et al., Environmental and Occupational Exposure Predictors of Multiple Chemical Sensitivity in Gulf War Veterans Assessed via a Validated Screening Instrument.
4. Sullivan et al., Neuropsychological functioning in Gulf War veterans potentially exposed to chemical weapons at Khamisiyah, Iraq.

Planned Manuscripts:

1. Sullivan et al., Cognitive Functioning in military pesticide applicators from the Gulf War.
2. Krengel et al., Health Symptom Report in pesticide applicators from the Gulf War.

Funding:

1. In June 2004, Drs. White, Krengel, Sullivan, and Proctor submitted a Merit Review grant application (Dr. White PI) to the Department of Veterans Affairs entitled "Structural Magnetic Resonance Imaging and cognitive correlates in Gulf War veterans." This study will further define neurological functioning in a previously followed cohort of treatment-seeking GW veterans. This grant was recommended for funding.

CONCLUSIONS:

Preliminary findings from the current study revealed that GW veterans exposed to varying levels of pesticides and PB continue to report health symptoms, including high blood pressure, cardiovascular disease, skin rashes, memory problems and stress reactions. Of interest, veterans who participated in the SRBI telephone surveys reported significantly more physical than emotional symptoms. It is of particular clinical relevance that these veterans continue to report significant physical symptoms and by documenting changes in cognitive status in conjunction with health concerns in this unique group of Gulf War veterans, the effects of exposure to neurotoxicants while in the Gulf will be further elucidated. This study will be able to confirm or disconfirm the conclusion of the OSAGWI health risk assessment and the RAND report which suggested that the acetylcholinesterase inhibiting pesticides including organophosphates and carbamates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans by performing cognitive assessments with a group of military pesticide applicators with known chemical exposures.

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APPENDIX:

For office use only

Structured Neurotoxicant Assessment Checklist

GENERAL HEALTH INFORMATION: (Please check the answer to these questions that best applies to you and your experiences)

MILITARY SERVICE

Please answer the following questions regarding your service career. For each type of service you were in, please complete the questions across that row. If you did not belong to that service, check the "No" response in the left column and move on to the next row.

	Branch of service (check all that apply):	How many years total were you on duty?	What years were you in this service?	What was the highest rank you achieved?	What was your primary MOS and military job title?
1. Have you ever served on **Active Military Duty**? _ Yes (if yes, continue with this row) _ No (if no, skip this row and go to the next row)	_ Army _ Air Force _ Navy _ Marines _ Other	(enter number of years on Active Duty in the box above)	List first and last year of service. From: To:	_ Enlisted _ NCO _ Officer	MOS: Military Job Title:
2. Have you ever served in the **Reserves**? _ Yes (if yes, continue with this row) _ No (if no, skip this row and go to the next row)	_ Army _ Air Force _ Navy _ Marines _ Other	(enter number of years on Reserve Duty in the box above)	List first and last year of service. From: To:	_ Enlisted _ NCO _ Officer	MOS: Military Job Title:
3. Have you ever served in the **National Guard**? _ Yes (if yes, continue with this row) _ No (if no, go to question #4)	_ Army _ Air Force _ Navy _ Marines _ Other	(enter number of years on National Guard Duty in the box above)	List first and last year of service. From: To:	_ Enlisted _ NCO _ Officer	MOS: Military Job Title:

4. **Were you ever deployed overseas during your military service?** _ No _ Yes ——→ If yes, where? _____

5. **Were you ever deployed or activated to serve domestically?** _ No _ Yes ——→ If yes, where? _____

6. **Were you ever in combat?** _ No _ Yes ——→ If yes, when? List years: _____

7. **Were you ever exposed to Agent Orange?** ——→ _ No _ Yes _ Not Sure

8. **Were you ever exposed to chemical or biological warfare agents during your military service?** _ No _ Yes _ Not Sure

9. **Were you ever given the anthrax vaccine during your military service?** ——→ _ No _ Yes _ Not Sure

   If yes, how many injections did you receive? ☐☐

10. **Have you ever taken pyridostigmine bromide (anti-nerve agent) pills?** ——→ _ No _ Yes _ Not Sure

    If yes, how many? ☐☐

OCCUPATIONAL EXPOSURE HISTORY:

Please indicate if you have ever been exposed to any of the materials listed in the far left column. Include time spent in military service.

Type of exposure:	**Examples of this type of exposure include:**	**Examples of work settings where exposure could occur:**	**Did you ever have a job where you were exposed?**	**If you think you were exposed or might have been,** list the first and last years you were working that (or those) job(s)?	**If yes,** was this exposure during your military job, civilian job, or both?	**Over that time,** how often would you say you were exposed? very often = every day often = 1-4 times/month sometimes = once/month to once/6 months rarely = once/year or less	**Did you wear personal protection when you were exposed?**
Solvents and Fuels	Trichloroethylene; Benzene; Gasoline; Paint Thinners; Diesel Fuel; Formaldehydes	Auto body repair or painting, Auto mechanic	_ Yes _ Don't Know _ No	From ☐☐☐☐ To ☐☐☐☐	_ Military _ Civilian _ Both	_ Very Often _ Often _ Sometimes _ Rarely	_ Yes _ No _ Sometimes
Petroleum Combustion Products	Gasoline, or Jet exhaust; Tent heaters; Oil/Chemical fires; Diesel Fuel	Auto/Truck mechanic; Oil delivery & services; Cold-weather camping	_ Yes _ Don't Know _ No	From ☐☐☐☐ To ☐☐☐☐	_ Military _ Civilian _ Both	_ Very Often _ Often _ Sometimes _ Rarely	_ Yes _ No _ Sometimes
Lead	Lead in paint; Soldering; Leadshot	Painting; Bridge repair; Radiator repair, Firing range	_ Yes _ Don't Know _ No	From ☐☐☐☐ To ☐☐☐☐	_ Military _ Civilian _ Both	_ Very Often _ Often _ Sometimes _ Rarely	_ Yes _ No _ Sometimes
Other Metals	Mercury; Arsenic; Cadmium	Thermometer makers; Copper smelting, Mining; Pesticide workers	_ Yes _ Don't Know _ No	From ☐☐☐☐ To ☐☐☐☐	_ Military _ Civilian _ Both	_ Very Often _ Often _ Sometimes _ Rarely	_ Yes _ No _ Sometimes
Pesticides	DDT; Diazinon; Malathion; Chlordane	Commercial farming, Pesticide application	_ Yes _ Don't Know _ No	From ☐☐☐☐ To ☐☐☐☐	_ Military _ Civilian _ Both	_ Very Often _ Often _ Sometimes _ Rarely	_ Yes _ No _ Sometimes

HOBBIES AND NON-OCCUPATIONAL EXPOSURES: (Please indicate if you have ever performed any of these activities in which you might have been exposed)

	Have you participated in this activity frequently over any 6 month period?	**If yes**, did you wear any personal protection during these activities, such as masks, boots, gloves, or other protective equipment?
1. Painting or Renovating your home	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes
2. Furniture Refinishing	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes
3. Auto Body Work	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes
4. Work with Glues, Solvents, or Chemicals (such as those used in model building, fiberglass repair, etc.)	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes
5. Pesticides while Gardening or Farming	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes
6. Jewelry Making, Pottery work, Studio painting	_ Yes, within the past 10 years _ Yes, but more than 10 years ago _ No	→ _ Yes _ No _ Sometimes